IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Søren MOURITSEN et al.	)	Group Art Unit: 1644
	)	
Application No.: 08/955,373	)	Examiner: Ronald B. SCHWADRON
	)	
Filed: October 21, 1997	)	
	)	
For: INDUCING ANTIBODY RESPONSE AGAINST SELF-PROTEINS WITH THE AID OF FOREIGN T-CELL EPITOPES	)	Confirmation No.: 7254
	)	

Attention: Mail Stop Appeal Brief-Patents
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Sir or Madam:

APPEAL BRIEF UNDER BOARD RULE § 41.37

In support of the Notice of Appeal filed March 15, 2012, and further to Board Rule § 41.37, Appellants present this Appeal Brief responding to the final rejection of claims 102, 103, 105, and 111 issued February 15, 2012. Payment of the $620.00 fee required under 37 C.F.R. § 1.17(c) and 37 C.F.R. § 41.20(b) accompanied the Notice of Appeal. This Appeal Brief is being filed concurrently with a petition for a one-month Extension of Time and the appropriate fee, thereby extending the due date to June 15, 2012. Accordingly, this Brief is timely filed.

If any additional fees are required or if the accompanying payment is insufficient, Appellants hereby authorize the USPTO to charge the required fees to **Deposit Account No. 50-5338**, referencing **Docket No. BNIT0003-PCT-US**.

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This Appeal Brief contains information organized and presented under the following subject matter headings according to the requirements of 37 C.F.R. § 41.37 and MPEP § 1206:

I. Real Party-In-Interest

The real party-in-interest for US Patent Application No. 08/955,373 (subject of the present Appeal) and owner of all right, title, and interest in the claimed invention is BN ImmunoTherapeutics, Inc. ('BNIT').

The present application was filed on October 21, 1997, and has been pending before Examiner Schwadron for more than fourteen years. BNIT acquired all right, title and interest in the claimed invention from Pharmexa A/S, a Danish biotechnology company, by an agreement effective February 20, 2009. Following that acquisition, Appellants substantially revised and simplified the pending claims, clarifying the subject matter of the claimed invention in an effort to bring prosecution to a productive close. Despite those efforts and an apparently productive telephone interview with the Examiner, however, prosecution failed to advance any closer to a conclusion, with an additional seven communications from the Examiner (one Restriction Requirement, two non-final Office Actions, two final Office Actions, and two Notices of Non-Compliant Amendment[1]) issuing over the next thirty-six months.

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1 The first Notice issued April 16, 2010, objecting to an obvious typographical error in withdrawn claims 92, 96 and 99 (the acronyms 'TNFα' and 'TNFβ' were erroneously entered as 'TNFa' and 'TNF|3'), even though the same error passed without objection in an Amendment and Response filed May 15, 2009.

The second Notice issued September 16, 2011, again objecting to an obvious typographical error, this time in withdrawn claim 88 (a comma added in a previous amendment was still shown as underlined text). The second Notice also indicated that '[n]ew drawings in response to the Office [A]ction of 7/14/99, paragraph 6 have never been filed.' Appellants note for the record that a Form PTO 948 pointing out defects in the originally-filed drawings and asking Appellants to submit new drawings was attached to the Non-Final Office Action mailed August 22, 1996. Examiner Schwadron reminded Appellants of the request to submit new drawings twice more, first in the Final Rejection mailed April 21, 1997, and again in the Non-Final Rejection mailed July 14, 1997. From that date, *over a period spanning more than twelve years of active prosecution by three different law firms*, during which twelve substantive office communications—including ten Office Actions and two Advisory Actions (not to mention numerous Restriction Requirements)—were issued, Examiner Schwadron never mentioned the request to submit new drawings again, until issuing the Notice of September 16, 2011.

Appellants note that these two Notices were mailed despite the Memorandum issued February 4, 2010, to the Patent Examiner Corps by Deputy Commissioner for Patents Peggy Focarino. That Memorandum reminded Patent Examiners of the desired practice of early inspection to identify minor errors early on in the examination process, and instructed them to help applicants correct such errors so that they do not hold up the substantive examination process.

II. Related Appeals and Interferences

There are currently no other appeals or interferences of which Appellants are aware that will directly affect, be directly affected by, or have any bearing on the Board's decision in the pending appeal.

III. Status Of Claims

Appellants/Applicants have filed a total of 112 claims during prosecution of this application. Claims 1-87 and 101 have been canceled. Claims 88–100, 104, 106–110, and 112 have been withdrawn from consideration as drawn to non-elected species. Claims 102, 103, 105, and 111 are pending and currently under final rejection. No claims are allowed.

Appellants hereby appeal the final rejection of claims 102, 103, 105, and 111. A listing of the claims on appeal is attached hereto as Appendix A, according to the provisions of 37 C.F.R. § 41.37(c)(1)(viii).

IV. Status Of Amendments

The Office Action mailed February 15, 2012 (the "Final Action"), finally rejecting claims 102, 103, 105, and 111, remains outstanding. The Final Action issued in response to Appellants' Amendment and Reply filed June 17, 2011, pursuant to 37 C.F.R. § 1.111, which included amendments to withdrawn claim 88 and pending claim 102. Those amendments appear to have been entered (although the Final Action does not explicitly indicate they were), since a prior rejection of claims 102, 103, 105, and 111 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement was withdrawn "in view of the amended claims." Final Action, page 2, item 2.

V. Summary Of Claimed Subject Matter

Independent claim 102 is directed to a method for inducing autoantibodies against a self-protein in a subject. The claimed method comprises a step of administering an analog of the self-protein made by molecular biological means, according to which one or more peptide fragments of the self-protein are substituted with one or more immunodominant foreign T-cell epitopes. The substitutions are made such that the secondary and tertiary structure of the self-protein is preserved to a large extent, in this manner creating a modified self-protein analog that induces an autoantibody response in the subject as shown by the production of antibodies which bind to the unmodified self-protein. The immunodominant foreign T-cell epitopes to be substituted for self-protein sequences are selected from those in ovalbumin, hen egg lysozyme, tetanus toxoid or diphtheria toxoid.

Dependent claims 103, 105, and 111 are drawn to specific embodiments of the method in which the one or more immunodominant foreign T-cell epitopes is an ovalbumin T-cell epitope generally (claim 103) or a specific ovalbumin T-cell epitope (claim 105), and in which the self-protein is tumor necrosis factor-alpha ("TNFα").

The claimed subject matter, with its functional limitation, finds support throughout the specification, published as US Patent Application Publication No. US 2002/0090379 A1 ("the '379 publication"), for example at:

> Paragraph [0011], disclosing that the surprising observations underlying the claimed invention are a consequence of the fact that the immunodominant foreign T-cell epitopes are inserted into the self-protein, against which it is the purpose to raise antibodies, in such a way that they substitute for the self-protein fragments, thereby preserving the overall secondary and tertiary structure of the self-protein to a large extent;
>
> Paragraph [0012], disclosing that the immunodominant foreign T-cell epitopes can be derived from tetanus toxoid;
>
> Paragraph [0017], disclosing that the substitution by molecular biological means of one or more peptide fragments in a self-protein by a corresponding number of immunodominant foreign T-cell

epitopes in such a way that the tertiary structure of the self-protein is essentially preserved renders the resulting self-protein analog highly immunogenic, leading to the induction of a profound antibody response against the unmodified self-protein that is not restricted to the known major histocompatibility complex ("MHC") type of the inserted immunodominant foreign T-cell epitopes;

Paragraph [0031], disclosing the preparation of self-protein analogs of ubiquitin and TNFα by the insertion of foreign T-cell epitopes 12-15 amino acids in length using genetic engineering methods and purification of such analogs, as well as production of autoantibodies against both ubiquitin and TNFα within one week after injection of the self-analogs emulsified in adjuvant into mice (*see also* Example 2 and Figures 1-2; as well as Example 3 and Figures 3-4);

Paragraph [0033], disclosing analogs of the self-proteins ubiquitin and TNFα produced by substitution of one or more peptide fragments by a corresponding number of peptides known to contain immunodominant T-cell epitopes, where the substitution is carried out so as to essentially preserve the overall tertiary structure of the original self-protein, and that it was possible to induce a fast and strong autoantibody response against such self-protein analogs even though the inserted foreign T-cell epitope was not restricted to the MHC molecules of the immunized mice;

Original claim 5, disclosing that the immunodominant foreign T-cell epitopes can originate from tetanus toxoid or diphtheria toxoid;

Example 1, disclosing molecular biological means for producing various self-protein analogs used in the claimed method;

Example 2 and Figures 1-2, disclosing the cloning strategy for producing ubiquitin analogs modified to include immunodominant foreign T-cell epitopes derived from ovalbumin or hen egg lysozyme, the purification of such analogs and their administration to mice, and the production of ubiquitin autoantibodies; and

Example 3 and Figures 3-4, disclosing the cloning strategy for producing TNFα analogs modified to include immunodominant foreign T-cell epitopes derived from ovalbumin or hen egg lysozyme, the purification of such analogs and their administration to mice, and the production of TNFα autoantibodies.

VI. Grounds of Rejection

The four grounds of rejection presented herein for review are set forth below.

A. Claims 102, 103, 105, and 111 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

B. Claim 102 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over International Publication No. WO 92/05192 A1 ("Russell-Jones"), in view of US Patent No. 5,716,596 ("Dean") and US Patent No. 5,969,109 ("Bona").

C. Claim 111 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Russell-Jones, in view of Dean and Bona as applied to claim 102, further in view of International Publication No. WO 93/05810 A1 ("Hellman") and US Patent No. 5,698,195 ("Le").

D. Claims 103 and 105 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Russell-Jones, in view of Dean and Bona as applied to claim 102, and further in view of US Patent Publication No. US 2003/0099634 A1 ("Vitiello").

VII. Argument

A. Rejection of claims 102, 103, 105, and 111 under 35 U.S.C. § 112, second paragraph.

The Examiner has finally rejected claims 102, 103, 105, and 111 as allegedly indefinite under 35 U.S.C. § 112, second paragraph. However, the Examiner has consistently failed to apply the correct legal standard when assessing definiteness of claim language under 35 U.S.C. § 112, second paragraph. Because the claims meet the definiteness requirement under the correct legal standard, the rejection must be reversed.

1. The correct legal standard for assessing definiteness of claim language under 35 U.S.C. § 112, second paragraph.

When reviewing a claim for compliance with the definiteness requirement of 35 U.S.C. § 112, second paragraph, "the examiner must consider the claim *as a whole* to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent." MPEP § 2173.02 (citing *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000)(emphasis added)).

Definiteness of claim language under 35 U.S.C. § 112, second paragraph, is not analyzed in a vacuum, but rather in light of:

(1) the content of the particular application disclosure;
(2) the teachings of the prior art; and
(3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

MPEP § 2173.02. The essential inquiry focuses upon "whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity." *Id.* Acceptability of claim language depends on whether one of ordinary skill in the art would understand what is claimed when the claims are read in light of the specification. *Id.* (citing *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.,* 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)).

2. The Examiner failed to apply the correct legal standard to assess definiteness of claim language under 35 U.S.C. § 112, second paragraph.

The Examiner did not apply the correct legal standard to assess definiteness of claim language under 35 U.S.C. § 112, second paragraph, in particular by failing to consider the claim as a whole and by ignoring the plain language of the claims, including the functional limitation recently added to further clarify the claim language in response to the indefiniteness objection. Most surprisingly, the Examiner impermissibly refused to accept no less than three separate Rule 1.132 declarations submitted, under oath, during more than a decade of prosecution, each one asserting that the meaning of the claims was clear to persons of ordinary skill in the art.

a. The Examiner's position regarding the claim language.

The Examiner alleged that the phrase "the secondary and tertiary structure of the self-protein is preserved to a large extent" renders claim 102 indefinite because "[i]t is unclear what changes to the secondary and tertiary structure would or would not be encompassed by the aforementioned term."[2] Final Action, section 4, page 2. The Examiner maintained this rejection *despite the plain language of the claim, which expressly recites "…such that said analog induces an autoantibody response as evidenced by antibody binding to the unmodified self-protein"*[3] *and despite the fact that previous responses made clear that the disputed claim language encompassed functional changes. Id.*; *see also* Amendment and Response filed May 15, 2009, at pages 8-9; and Amendment and Reply filed June 17, 2011, at page 8.

Ignoring the functional limitation of the claim, the Examiner asserted that "it is unclear if this term encompasses changes at the physical/chemical level (*e.g.* crystal structure) or simply functional changes (*e.g.* still immunogenic antigen as evidenced by antibody binding by antibodies

2 Claims 103, 105, and 111 all depend directly or indirectly from claim 102, and therefore incorporate by reference all elements of that claim, although they do not themselves recite the phrase "the secondary and tertiary structure of the self-protein is preserved to a large extent" to which the Examiner objects. Applicants assume that claims 103, 105, and 111 have been rejected under 35 U.S.C. § 112, second paragraph for that reason, and note therefore that all arguments relating to the definiteness of amended claim 102 also apply to claims 103, 105, and 111.

3 Claim 102 was added by amendment in the Amendment and Response filed May 15, 2009; withdrawn claim 88 was similarly amended to incorporate identical language.

specific for unmodified antigen)" and further speculated that "[i]f the term is interpreted as encompassing changes at the physical/chemical level, it is unclear as to what deviations from the normal crystal structure would or would not be encompassed" by the disputed claim term. *Id.*

The Appellants respectfully disagree because, contrary to the Examiner's reading of the claim, the plain language unambiguously informs a person of skill in the art about the type of changes the claim encompasses, *i.e.,* functional changes. In particular, the *modified* self-protein analog covered by the claim must induce an autoantibody response in the subject (*i.e.,* it must be immunogenic) as evidenced by antibody binding to the *unmodified* self-protein.

Certainly, if the term is interpreted as encompassing 'functional changes', by the Examiner's own argument (as set forth repeatedly during more than a decade of prosecution), the structural (*i.e.*, physical/chemical) nature and extent of deviations from the secondary and tertiary structure of the self-protein need not be specified. Instead, it is sufficient if the modified self-protein analog remains immunogenic, as shown by the binding of the induced autoantibodies to the unmodified self-protein (or as the Examiner phrased it, "still immunogenic antigen as evidenced by antibody binding by antibodies specific for unmodified antigen"). Final Action, section 4, page 2.

Nonetheless, in the Final Action, the Examiner summarily dismissed the plain language of the claim, Appellants' arguments that the claim language was definite under 35 U.S.C. § 112, second paragraph, and three declarations on that point, asserting only that "the fact that the analog induces an antibody response does not define what changes to the secondary and tertiary structure would or would not be encompassed by the aforementioned term." Final Action, item 4, page 4. This despite the fact that the Examiner previously stated several times that disclosure "as to what deviations from the normal crystal structure would or would not be encompassed" by the phrase "to a large extent" is required "[i]f the term is interpreted as encompassing changes at the physical/chemical level" but not if the term encompassed "functional changes". Final Action, item 4, page 2. In furtherance of

his circular reasoning, the Examiner observed that "the phrase 'large extent' is not defined in the specification and has no art recognized meaning in the context recited in the claims" and concluded "[a]ssuming arguendo that it was clear as to what changes were encompassed by preserving the secondary and tertiary structure, it would still be unclear as to what changes did or did not encompass a 'large extent'." Final Action, section 4, page 3.

The Appellants respectfully disagree because, as previously emphasized, that particular 'term' within the 'phrase' is functionally defined in the claim itself and there cannot be any doubt that a person of skill in the art could easily confirm by standard methods known in the art whether the modified self-protein analog remains immunogenic, as shown by the binding of the induced autoantibodies to the unmodified self-protein.

b. The Examiner's position regarding the Rule 1.132 declarations.

The Examiner's peremptory dismissal of three separate declarations submitted during prosecution, under oath, by persons having ordinary skill in the art deserves particular attention.[4] The Examiner not only ignored relevant portions of the declarations but also took other portions out of context, as set forth in more detail below. Ultimately, the Examiner erroneously concluded that Appellants' "own declarants cannot agree as to what the phrases 'essential preservation of overall tertiary structure' or 'essentially preserve the secondary structure and tertiary structure' mean or encompass". Final Action, item 4, page 4 (original emphasis omitted). The Appellants respectfully disagree and request that these declarations be appropriately considered in this proceeding, as they confirm that the pending claims meet the definiteness requirement.

4 The declarations filed include: (i) the Declaration of Professor Sven Frøkjaer, Ph.D., accompanying a Preliminary Amendment filed August 19, 1998; (ii) the Declaration of Dr. Paul Travers, accompanying a Response to Final Rejection filed October 9, 2000; and (iii) the Declaration of Alain Delcayre under 37 C.F.R. § 1.132 , accompanying the Amendment and Reply filed November 24, 2010.

3. Claims 102, 103, 105, and 111 comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph.

Claims 102, 103, 105 and 111 comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph, because the plain language of the claims apprises one of ordinary skill in the art of their scope, when read as a whole in view of the content of the application disclosure and the teachings of the prior art, thereby satisfying the notice function required by statute.

a. The plain language of the pending claims apprises one skilled in the art reading the claims as a whole of their scope.

The plain language of the pending claims apprises one skilled in the art reading the claims as a whole of their scope. Indeed, claim 102 explicitly makes clear that the phrase "the secondary and tertiary structure of the self-protein is preserved to a large extent" is indeed functionally limited, or—adopting the Examiner's somewhat confusing terminology (see Section VII.A.1.b. above)—that the claim encompasses "functional changes" to the secondary and tertiary structure of a modified self-protein analog.

Claim 102 recites:

> [a] method for inducing autoantibodies against a self-protein in a subject, said method comprising:
> administering to the subject an analog of the self-protein made by molecular biological means, wherein said analog is made by substituting one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes selected from ovalbumin, hen egg lysozyme, tetanus toxoid, or diphtheria toxoid T-cell epitopes,
> such that the secondary and tertiary structure of the self-protein is preserved to a large extent; *such that said analog induces an autoantibody response as evidenced by antibody binding to the unmodified self-protein*

(emphasis added).

Thus, according to the plain language of the claim, the secondary and tertiary structure of a self-protein analog is preserved to a large extent where: (1) the self-protein analog induces an autoantibody response in a subject; and (2) the induced autoantibodies bind to the corresponding

unmodified self-protein. Therefore pending claim 102, as well as claims 103, 105, and 111 depending therefrom, apprise one skilled in the art reading the claims as a whole of their scope—the secondary and tertiary structure of a self-protein is preserved to a large extent when those two criteria are satisfied—thereby serving the notice function required by statute.

Moreover, the plain language of the claim makes clear that (1) the disputed claim language is functionally limited, or in the Examiner's words, encompasses 'functional changes' to the secondary and tertiary structure of a self-protein, not 'changes at the physical/chemical level'; and in particular since (2) such functional changes are explicitly defined to encompass "induc[ing] an autoantibody response as evidenced by antibody binding to the unmodified self-protein[,]" it renders the inquiry about the structural nature and scope of any changes to the secondary and tertiary structure of the self-protein entirely moot.

For at least this reason, claims 102, 103, 105, and 111 comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph, and therefore the Examiner's rejection must be reversed.

b. The pending claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity.

As noted above, the essential definiteness inquiry focuses upon "whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity." MPEP § 2173.02. Acceptability of claim language depends on whether one of ordinary skill in the art would understand what is claimed, when reading the claims in light of the specification. *Id.* (citing *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.,* 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)). Accordingly, "a claim term that is not . . . defined in the specification is not indefinite if the meaning of the claim term is discernible." *Id.* (citing *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372, 69 USPQ2d 1996, 1999-2000 (Fed. Cir. 2004)).

Appellants have emphasized more than once during prosecution that the disputed claim language is functionally defined or—adopting the Examiner's terminology—encompasses simply 'functional changes' rather than changes at the physical/chemical level. Moreover, Appellants have also consistently averred that the scope of the claim is functionally limited.[5] Hence, the nature and extent of the structural changes need not be defined in the claims because it is clear from the plain language of the claims that a modified self-protein analogue—*meaning simply one in which the secondary and tertiary structure is preserved to a large extent*—must be able to induce an autoantibody response as shown by antibody binding to the corresponding unmodified self-protein. The Appellants simply cannot explain the Examiner's persistent disregard of the plain language of the claim, which explicitly refers to functional changes, insisting instead that the claim term is indefinite because it is unclear whether the claim language encompasses "changes at the physical/chemical level or simply functional changes[.]" Appellants respectfully submit that this basis for the rejection is nonsensical and should be disregarded.

The Examiner's circular reasoning rejecting the claims as indefinite because "the fact that the analog induces an antibody response does not define what changes to the secondary and tertiary structure would or would not be encompassed by the aforementioned term" is equally unconvincing. Final Action, item 4, pages 3-4. In particular, the Examiner's argument that the claims are indefinite because "[t]he phrase 'large extent' is not defined in the specification and has no art recognized meaning in the context recited in the claims" lacks merit. Final Action, item 4, page 3.

First of all, the meaning of the phrase "large extent" is clearly discernible when reading the claims in light of the specification, as the applicable legal standard requires. As noted above "a claim term that is not . . . defined in the specification is not indefinite if the meaning of the claim term is

5 Appellants also note that "[t]here is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper." MPEP § 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971)).

discernible." MPEP § 2173.02 (citing *Bancorp Services, L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1372, 69 USPQ2d 1996, 1999-2000 (Fed. Cir. 2004)). In this case, the meaning of the phrase 'large extent' is discernible not only from the plain language of the claims (as discussed above), but also from the specification, in light of which the claims must be read, even though the phrase is not expressly defined therein. For example, as the specification explains, the observations described in the present patent application were "a consequence of the fact that the T-cell epitopes are inserted into the self-protein, against which it is the purpose to raise antibodies. The epitopes substitute the self-protein fragments, thus preserving the overall secondary and tertiary structure of the self-protein to a large extent." US Patent Publication No. US 2002/0090379 A1, at page 2, paragraph 11. Moreover, the specification also makes clear that preservation of the secondary and tertiary structure of the self-protein analogues is important "because these structures determine the specific recognition of the non-modified self-protein by the induced antibodies." *Id.*

The relevant inquiry is whether a person of skill in the art employing standard methods or methods taught in the specification can assess and thereby confirm the particular functional characteristics defining the claim scope, *i.e.,* whether the modified self-protein analog remains immunogenic, as shown by the binding of the induced autoantibodies to the unmodified self-protein. The indisputable answer to such inquiry is yes. For further details, *see, e.g.*, Declaration of Professor Sven Frokjaer, Ph.D., accompanying a Preliminary Amendment filed August 19, 1998; Declaration of Dr. Paul Travers, accompanying a Response to Final Rejection filed October 9, 2000; and Declaration of Alain Deleayre under 37 C.F.R. § 1.132 , accompanying the Amendment and Reply filed November 24, 2010.

Consequently, pending claims 102, 103, 105, and 111 set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity such that one of ordinary skill in the art would understand what is claimed, when reading the claims in light of the specification.

MPEP § 2173.02 (citing *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.,* 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)). For at least these reasons, claims 102, 103, 105, and 111 comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph, and therefore the Examiner's rejection must be reversed.

c. The pending claims are definite because three persons of ordinary skill in the art declared, under oath, that they understood what is claimed, in light of the specification.

Finally, acceptability of claim language depends on whether one of ordinary skill in the art would understand what is claimed, when the claims are read in light of the specification. MPEP §2173.02 (citing *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.,* 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)). Appellants have amply demonstrated during prosecution that one of ordinary skill in the art would understand what is claimed, when reading the claims in light of the specification, having submitted Declarations from three individuals of at least ordinary skill in the art, each independently concluding that the disputed claim term/phrase was definite and would be understood by a person of skill in the art.

Nevertheless, the Examiner has refused to accept any of their conclusions,[6] instead erroneously arguing that the "declarants cannot agree as to what the phrases 'essential preservation of overall tertiary structure' or 'essentially preserve the secondary structure and tertiary structure' mean or encompass",[7] while ignoring relevant portions of the declarations and taking other portions out of context. Final Action, item 4, page 4 (emphasis omitted). Even without considering the fact

6 The declarations filed include: (i) the Declaration of Professor Sven Frøkjaer, Ph.D., accompanying a Preliminary Amendment filed August 19, 1998; (ii) the Declaration of Dr. Paul Travers, accompanying a Response to Final Rejection filed October 9, 2000; and (iii) the Declaration of Alain Delcayre under 37 C.F.R. § 1.132 , accompanying the Amendment and Reply filed November 24, 2010.

7 Appellants have consistently argued throughout prosecution that both phrases are definite under 35 U.S.C. § 112, second paragraph. Moreover, the Examiner agreed that either formulation of claim language raised the same issues with respect to the statute (*see, e.g.*, Amendment and Reply to Office Action filed June 17, 2011, at Section IV.A., page 9).

that the functional limitation is clear from the plain language of the claim, the Examiner's position with respect to the three Declarations submitted under oath is untenable.

Moreover, the implication that the Declarations are not relevant because "none of said declarations address the newly added limitation of the claim that the secondary and tertiary structure is 'preserved to a large extent'[,]" which Appellants amended to its current form expressly at the Examiner's suggestion and which mirrors the wording in the specification, is nonsensical. Final Action, item 4, page 3.

The Examiner cannot have it both ways. Claim 102, currently rejected as allegedly indefinite, recites ". . . such that the secondary and tertiary structure of the self protein is preserved to a large extent[.]" Final Action, item 4, page 2. Previous versions of claim 102 reciting "…such that the secondary and tertiary structure of the self-protein *is essentially preserved*" were pending for much of the application's pendency, but were rejected on the same grounds, based on identical arguments. *See, e.g.*, Office Action of February 17, 2011, item 7, page 3.

In a telephone interview conducted April 27, 2011 (*see, e.g.*, Amendment and Reply to Office Action filed June 17, 2011, at Section IV.A., page 9), Examiner Schwadron indicated that *either* formulation of claim 102 would raise similar issues 35 U.S.C. § 112, ¶2 for alleged indefiniteness. The Examiner's objection to the Declarations for [explicitly] failing to address the newly added limitation was raised specifically to the Travers Declaration (Final Action, item 4, page 3, stating "[re]garding the first Travers Declaration, said declaration addresses the phrase 'essentially preserve the overall tertiary structure' wherein said phrase is not currently recited in the claims under consideration") and generally to all three Declarations (Final Action, item 4, page 3, stating "none of said declarations address the newly added limitation that the secondary and tertiary structure is 'preserved to a large extent'"). The Appellants understand both limitations "essentially preserved"

and "to a large extent" to have the same meaning and assert that both terms are clearly understood by a person of skill in the art reading the claims in light of the specification.

The claim is functionally defined and that is the relevant limitation to the scope of the claim. The Examiner has no valid basis to disregard the previously submitted Declarations regarding definiteness simply because one term in the claims not used identically in the specification was substituted for its equivalent term actually used *in ipsis verbis* in the specification. Accordingly, the Examiner's objection regarding the Declarations should be disregarded.

i. The Frøkjaer Declaration.

The first Declaration, submitted by Professor Sven Frøkjaer, Ph.D.[8], accompanied a Preliminary Amendment filed August 19, 1998 (the "Frøkjaer Declaration"). As Dr. Frøkjaer explained,

> it is important to preserve the overall tertiary structure of the original self-protein in order to optimize its therapeutic effect. Indeed, a change in tertiary structure of a self-protein would increase the risk of inducing antibody responses to sequentially native regions of the protein now having a changed structure, and not only to remaining native and amino acid sequence modified regions.

Frøkjaer Declaration, at page 2, paragraph 3. Dr. Frøkjaer further attested that

> [i]t is my understanding, as a person of skill in the art of protein and peptide formulation, that the self-protein analog, having a preserved tertiary structure, can be prepared by selecting peptides comprising appropriate immunodominant epitopes, exchanging peptides [*sic*] sequences of essentially the same length in various parts of the self-protein molecule and determining the raised antibody response by suitable assay techniques

Frøkjaer Declaration, at page 2, paragraph 4.

Thus, Dr. Frøkjaer, one of at least ordinary skill in the art, understood the allegedly indefinite claim language in functional terms[9]—adopting the Examiner's terminology—to mean that a self-

8 Dr. Frøkjaer worked for many years as a scientist both in the pharmaceutical industry and academia, and therefore is qualified as one of ordinary skill in the art, if not an expert.

protein analog modified to include one or more foreign T cell epitopes had an essentially preserved secondary and tertiary structure if it induced an autoantibody response against the corresponding unmodified self-protein. Obviously, Dr. Frøkjaer also understood that the autoantibody response would have to be measured by standard assays (*i.e.*, enzyme-linked immunosorbent assays, or ELISAs).

Rather than addressing Dr. Frøkjaer's clear statement regarding the meaning of the disputed claim term, the Examiner focused instead on Dr. Frøkjaer's assertion that use of "screening procedures" employing "standard experimental techniques" known in the art "would be necessary" to determine whether the secondary and tertiary structure of the self-protein has been essentially preserved or preserved to a large extent. *See, e.g.*, Final Action, item 4, page 4; and Frøkjaer Declaration, pages 2-3, paragraph 5. Because neither subsequent declarant mentioned the possibility of screening self-protein analogues, which indisputably is standard technique in the field, the Examiner inexplicably concluded that "applicants [sic] own declarants cannot agree as to what the phrases 'essential preservation of overall tertiary structure' or 'essentially preserve the secondary and tertiary structure' mean or encompass" and that "the limitation under consideration has no art recognized meaning." Final Action, at item 4, page 4. Noting that all functional claim limitations require some kind of screening or determination of characteristics, the Appellants respectfully disagree with the Examiner's unsupported inference.

ii. The Travers Declaration.

The second Declaration, submitted by Dr. Paul Travers[10] on October 9, 2000, accompanied a Response to the Final Rejection mailed May 2, 2000 (the "Travers Declaration"). Dr. Travers

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9 Appellants note that "[t]here is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper." MPEP § 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971)).

10 Dr. Travers worked for many years as an academic scientist, and therefore qualified as one of ordinary skill in the art, if not an expert. Travers Declaration, at page 1, paragraph 1.

noted that "[i]n paragraph 4 in the Office Action of 2 May 2000, the Examiner states that he finds the recitation of 'essentially preserve the overall tertiary structure' unclear. *It is my opinion as a skilled practitioner that this is not the case.*" Travers Declaration, at page 1, paragraph 4 (emphasis added). Dr. Travers further stated that *"[i]t is my opinion that the wording 'essentially preserve [the] overall tertiary structure' as used in the above-captioned patent application can be readily understood by the skilled reader.*" Travers Declaration, at page 2, paragraph 6 (emphasis added).

Dr. Travers further explained that the specification made clear that the 'essential preservation of overall tertiary structure' meant that "when a peptide containing a T-cell epitope is substituted into a self-protein according to the above-captioned patent application, the substitution is one which introduces a minimum of disturbance in the tertiary structure of the self-protein whereby a maximum number of B-cell epitopes are preserved when comparing to the unmodified self-protein." Travers Declaration, at page 2, paragraph 6.

Thus, Dr. Travers, a second person of at least ordinary skill in the art, understood the allegedly indefinite claim language to mean, in functional terms—again adopting the Examiner's terminology—that a self-protein analog modified to include one or more foreign T cell epitopes had a preserved tertiary structure if the modification induced minimal tertiary structural changes in the native protein such that a maximum number of B-cell epitopes were preserved compared to the unmodified self-protein. As one of ordinary skill in the art would know, preservation of a maximum number of B-cell epitopes is important because the autoantibodies induced by vaccination with the modified self-protein analogues must bind the unmodified self-protein.

However, the Examiner ignored Dr. Travers' unambiguous opinions as a skilled practitioner, stating only that "said declaration addresses the phrase 'essentially preserve the overall tertiary structure' wherein said phrase is not currently recited in the claims under consideration[,]" inaccurately inferring that "applicants [sic] own declarants cannot agree as to what the phrases

'essential preservation of overall tertiary structure' or 'essentially preserve the secondary structure and tertiary structure' mean or encompass." Final Action, item 4, page 4. The Examiner lacks basis for such conclusion and the Appellants respectfully disagree.

iii. The Delcayre Declaration.

Most recently, Appellants submitted the Declaration of Alain Delcayre[11] under 37 C.F.R. § 1.132 with the Amendment and Reply filed November 24, 2010 (the "Delcayre Declaration"). Like Dr. Frøkjaer and Dr. Travers before him, Dr. Delcayre asserted that the meaning of the disputed claim language was clear to a person of skill in the art. Indeed, based on the plain language of the claim and the disclosure of the specification, Dr. Delcayre understood that the secondary and tertiary structure of a self-protein analog is essentially preserved where: (1) the self-protein analog induces an autoantibody response in a subject; and (2) the induced autoantibodies bind to the corresponding unmodified self-protein. Delcayre Declaration, ¶¶5-6. The Examiner responded to the Delcayre Declaration and accompanying arguments in the same fashion as in previous Office Actions, by continuing to insist that it is unclear what sort of changes to the secondary and tertiary structure of the self-protein would be encompassed by the disputed claim language—even though still another person of at least ordinary skill in the art declared under oath, for the third time, that the meaning of that language was clear.

Thus, contrary to the assertions of not one, not two, but *three separate Declarants* having at least ordinary skill in the art stating that the meaning of the disputed claim term was clear and definite, the Examiner maintains that it is unclear what sort of changes to the secondary and tertiary structure of the self-protein would be encompassed by the disputed claim term. Given the plain

11 Dr. Delcayre has conducted vaccine- and immunotherapy-related research for more than twenty years and therefore qualifies as one of at least ordinary skill in the art in those fields. He has been employed by the current assignee of the application since 2005 and was thus an employee of the assignee at the time of its acquisition in 2009. This application has been pending in its current form since October 21, 1997, although it is a continuing prosecution application claiming priority to an international application filed on August 25, 1994. Delcayre Declaration, ¶¶1-2.

language of the claim, explicitly referencing particular functional changes defining its scope, and the fact that three separate Declarations by persons having at least ordinary skill in the art each independently concluded that the disputed claim term is definite, it remains unclear to Appellants exactly why the Examiner continues to insist that it is unclear whether the claim language encompasses "changes at the physical/chemical level or simply functional changes[.]"

Appellants reiterate that one skilled in the art—such as, for example, any one of Drs. Frøkjaer, Travers, or Delcayre—would understand the disputed claim term to encompass particular functional changes that correlate to the secondary and tertiary structure of a self-protein, such that the induced autoantibodies will bind the unmodified self-protein. Consequently, it is not necessary to define the nature and scope of the changes to the secondary and tertiary structure of the self-protein analog, despite the Examiner's repeated assertions to the contrary.

For at least this reason, claims 102, 103, 105, and 111 comply with the definiteness requirement of 35 U.S.C. § 112, second paragraph, and therefore the Examiner's rejection must be reversed.

B. Rejection of Claim 102 under 35 U.S.C. § 103(a).

The Examiner rejected claim 102 under 35 U.S.C. § 103(a) as allegedly obvious over WO 1992/005192 ("Russell-Jones") in view of US Patent No. 5,716,596 ("Dean") and US Patent No. 5,969,109 ("Bona"). Because the Examiner failed to establish a *prima facie* case of obviousness, the rejection must be reversed.

1. The Examiner's position regarding Russell-Jones, Dean and Bona.

The Examiner alleged that Russell-Jones teaches "the claimed method except for use of immunodominant foreign T cell epitopes derived from diphtheria toxoid," that Bona teaches "that a T cell epitope can be substituted into a particular region of a target molecule wherein the T cell epitope retains immunogenicity," and that Dean teaches that somatostatin is a self-protein because

of its recognized role in a variety of diseases. Final Action, item 8, page 6. Based on those teachings, the Examiner concluded that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention[,]" and that a skilled artisan would have been motivated to combine those alleged teachings to arrive at the claimed invention "because immunodominant foreign T cell epitopes derived from diphtheria toxoid were known in the art and diphtheria toxoid was already approved as a carrier for human vaccines." *Id.* Additionally, the Examiner asserted that "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." Final Action, item 8, page 10 (internal citation and original emphasis omitted).

The Appellants respectfully disagree and because the Examiner has failed to establish a *prima facie* case of obviousness as discussed in more detail below, the rejection must be reversed.

2. The Examiner has not established a *prima facie* case of obviousness because the cited references do not provide a motivation to combine the prior art to achieve the claimed invention.

To reject a claim as *prima facie* obvious under 35 U.S.C. § 103(a), the Examiner must show that there was some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify or combine the prior art reference teachings to arrive at the claimed invention.[12] MPEP § 2143. The Examiner's showing must be sufficient to conclude that "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." MPEP

12 The rationale underlying the rejections under 35 U.S.C. § 103(a) remains somewhat unclear. Initially, the Examiner apparently applied the so-called 'teaching, suggestion, or motivation' test (Rationale 'G', MPEP § 2143)—at least in part, but in responding to Appellants arguments, he later mentioned the 'use of known techniques to improve similar devices, methods or products in the same way' rationale (Rationale 'C', MPEP § 2143) and appeared to apply the latter in combination with the former. *See, e.g.*, Final Action, item 8, page 10. Because the Examiner did not establish a *prima facie* case of obviousness under either rationale, Appellants do not respond separately to the obviousness rejection based on rationale 'C'.

§ 2143 (quoting *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006)). Moreover, the Examiner must review the cited references without the benefit of impermissible hindsight vision afforded by the claimed invention. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986)(internal citations omitted).

In this case, the Examiner has not met his burden to establish *prima facie* obviousness because the cited references do not provide a motivation to combine the prior art to achieve the claimed invention.

a. Russell-Jones does not "teach the claimed method except for the use of immunodominant foreign T cell epitopes derived from diphtheria toxoid".

Russell-Jones does not "teach the claimed method except for the use of immunodominant foreign T cell epitopes derived from diphtheria toxoid," because the pending claims recite "method[s] for inducing autoantibodies against a self-protein in a subject[.]" On the contrary, Russell-Jones discloses only: (1) the *insertion* of foreign T-cell epitopes into self- and non-self proteins; and (2) the substitution of immunosuppressive domains in a protein from human immunodeficiency virus ("HIV")—a non-self protein—with foreign T-cell epitopes, as discussed in more detail below.

Virtually all of the disclosure in Russell-Jones—including the passages cited by the Examiner—contemplates raising immune responses against various immunogens[13] by administration of immunogen-carrier conjugates where the immunogens are attached to the carrier either by chemical coupling or by recombinant DNA methods (*i.e.*, in the form of fusion proteins), or by administration of immunogens into which isolated T-cell epitopes have been *inserted*. In sharp contrast, the claimed methods employ self-protein analogs in which heterologous T-cell epitopes are

13 Appellants note Russell-Jones does indicate that in some cases the immunogens can be self-proteins, specifically disclosing hormones such as luteinizing hormone, somatostatin, follicle-stimulating hormone, and inhibin. Russell-Jones, at page 9, lines 13-26.

substituted for amino acid sequences in a self-protein. *See, e.g.*, Russell-Jones, page 8, lines 30-35; page 9, lines 13-26; page 31, Example 4 and Abstract. The Appellants' approach is entirely different.

The only disclosure in Russell-Jones even vaguely relating to the pending claims—which recite self-protein analogs "made by *substituting* one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes"—is a prophetic example describing the replacement of suppressor T-cell epitopes in a viral (*i.e.*, non-self) antigen with heterologous T-cell epitopes derived from TraT protein in an effort to stimulate an immune response against the immunosuppressive gp120 protein from type I human immunodeficiency virus ("HIV-1"). Russell-Jones, at page 31, Example 5. Because the antigen to be used in this prophetic example—the HIV-1 gp120 protein—was derived from a foreign pathogen, any anti-gp120 antibodies induced by the gp120 analogue would not be autoantibodies.

Nor does Russell-Jones disclose or recognize the importance of preserving the secondary and tertiary structure of the modified self- (or non-self) protein to a large extent. Instead, Example 5 discloses only that removal of T-cell epitopes which actually suppress T-cell activity *may* induce antibody responses to *non-self* antigens. Indeed, the fact that the vast majority of the disclosure in Russell-Jones—save for the prophetic disclosure of Example 5—describes the *insertion* of T-cell epitopes into self- and non-self proteins rather than the *substitution* of T-cell epitopes for native sequences in self-proteins strongly suggests that Russell-Jones did not appreciate that preserving the secondary and tertiary structure of the self-protein analogues was at all relevant to the invention disclosed therein.

Therefore Russell-Jones does not "teach the claimed method except for use of immunodominant foreign T cell epitopes derived from diphtheria toxoid," because it does not teach or suggest methods for inducing autoantibodies against a self-protein in a subject by administering *a*

self-protein analog made by *substituting* one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes.

Moreover, hindsight determinations are not permitted when assessing obviousness. MPEP § 2142. Since Russell-Jones must be reviewed without the benefit of impermissible hindsight afforded by the claimed invention, its disclosure must be read and understood from the perspective of a person of skill in the art as of the application's priority date of August 25, 1994, and the Examiner's argument therefore has no basis. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986)(internal citations omitted).

For at least this reason, claim 102 is not obvious over Russell-Jones in view of Dean and Bona, and therefore the Examiner's rejection must be reversed.

b. Russell-Jones teaches away from the use of heterologous T-cell epitopes derived from diphtheria toxoid or tetanus toxoid.

Patents and patent applications are relevant as prior art for all they disclose, and must be considered in their entirety, including portions that would teach away from the claimed invention. MPEP § 2123 (citing *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (stating that patent references "are part of the literature of the art, relevant for all they contain")); *see also* MPEP § 2141.02(VI) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)).

The Examiner continued to allege that motivation to combine references can be found in Russell-Jones' disclosure that "immunodominant foreign T cell epitopes derived from diphtheria toxoid *were known in the art* and that diphtheria toxoid *was already approved as a carrier for human vaccines*." Final Action, item 8, page 9. However, the Examiner once again ignored additional disclosure in Russell-Jones that actually teaches away from the use of heterologous T-cell epitopes derived from diphtheria toxoid ("DT") or tetanus toxoid ("TT")(*see, e.g.*, pages 11-12 of the Amendment and

Response filed November 24, 2010). Because Russell-Jones discloses: (1) that TraT conjugates and TraT-derived peptides induce a superior T-cell response compared to DT conjugates and DT-derived peptides; (2) that neither DT nor TT were selected for use as immunologic carriers because they had useful immunostimulatory characteristics; and (3) that commonly-used TT and DT carriers can lead to immunological complications, *the reference clearly teaches away from the use of DT conjugates or DT-derived peptides in vaccines or other immunotherapeutics.* Accordingly, Russell-Jones would not motivate one of ordinary skill in the art to combine its disclosure with that of Dean and Bona.

For at least this reason, claim 102 is not obvious over Russell-Jones in view of Dean and Bona, and therefore the Examiner's rejection must be reversed.

c. The disclosure of Dean and Bona does not remedy the deficiencies of Russell-Jones.

The Examiner cited Bona for allegedly teaching "that a T cell epitope can be substituted into a particular region of a target molecule wherein the T cell epitope retains immunogenicity." Final Action, item 8, pages 6-7. Bona describes the production of chimeric antibodies to which heterologous T- or B-cell epitopes have been added. Such antibodies are intended for use in methods of treating diseases caused by foreign pathogens (*e.g.*, influenza or HIV-1) and for treatment of neoplasms. *Crucially, the heterologous epitopes are derived from foreign pathogens, and are used to stimulate or enhance a T- or B-cell response* ***directed to the chimeric antibody*** *(i.e., a non-self protein), rather than to induce the production of autoantibodies to a self-protein. See, e.g.*, Bona, col. 20:35 to col. 21:25. Thus, neither Russell-Jones nor Bona discloses methods of producing autoantibodies to self-proteins by *substituting amino acid sequences from the self-proteins* with heterologous T-cell epitopes like the presently claimed methods.

The Examiner cited Dean simply for teaching that somatostatin is a self-protein because of its recognized role in a variety of diseases. Final Action, item 8, page 7. Dean describes the

production of radiolabeled peptide derivatives and analogs of somatostatin for use as imaging and therapeutic agents, and does not mention vaccines at all. *See, e.g.*, Dean, col. 3:54-64. Inventions in all fields can consist of different elements previously disclosed and recognized in the art yet still be patentable because they are combined or used in a novel and non-obvious way. The reliance on Dean in this case from a completely different field of use should be disregarded, as it lacks relevance for an assessment of obviousness in the present case.

Because neither Dean nor Bona remedies the deficiencies of Russell-Jones, none of the cited references provide one skilled in the art the motivation to combine the teachings of Russell-Jones, Dean, and Bona to arrive at the claimed invention. Consequently, the Examiner has not established a *prima facie* case of obviousness.

For at least this reason, the rejection of claim 102 as allegedly obvious over Russell-Jones in view of Dean and Bona must be reversed.

3. The Examiner has not established a *prima facie* case of obviousness because one of ordinary skill in the art would not have a reasonable expectation of success to arrive at the claimed invention by combining the cited references.

Furthermore, the Examiner has not established a *prima facie* case of obviousness because none of the cited references, either alone or in combination, provides **any** expectation of success—much less a reasonable expectation of success as required by section 2143 of the MPEP—to arrive at the claimed invention. Appellants reiterate that none of the cited references provides any expectation of success *because none of the references describes actually making a modified self-protein containing one or more T-cell epitopes substituted into the self-protein such that the secondary and tertiary structure of the self-protein is preserved to a large extent and using it to induce autoantibodies to the self-protein*. As of the August 25, 1994, priority date, this approach was novel and non-obvious.

As discussed above, the only disclosure in Russell-Jones even vaguely relating to the subject matter of the pending claims—which recite self-protein analogs "made by *substituting* one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes"—is a prophetic example describing the replacement of suppressor T-cell epitopes *in a viral (i.e., non-self) antigen* with heterologous T-cell epitopes derived from TraT protein in an effort to stimulate an immune response against the immunosuppressive gp120 protein from type I human immunodeficiency virus ("HIV-1"). Russell-Jones, at page 31, Example 5. Similarly, the only potentially relevant disclosure in Bona describes the production of chimeric antibodies to which heterologous T- or B-cell epitopes derived from foreign pathogens have been added in order to stimulate or enhance a T- or B-cell response *directed to the chimeric antibody (i.e., a non-self protein)*, rather than to induce the production of autoantibodies to a self-protein. *See, e.g.*, Bona, col. 20:35 to col. 21:25.

Thus, none of the cited references can provide any expectation that a modified self-protein made by substituting one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes would induce an autoantibody response to the unmodified self-protein as recited in the pending claims. Only Appellants' specification provides a reasonable expectation of success.[14]

For at least this additional reason, the rejection of claim 102 under as allegedly obvious over Russell-Jones in view of Dean and Bona must be reversed.

14 The Examiner responded to this argument only with the nonsensical statement that "[w]ith regards to reasonable expectation of success, the prior art teaches/renders obvious the claimed invention and is therefore as enabled as the instant application." Final Action, item 8, pages 7-8.

4. The rebuttal evidence of unexpected results is related to the claimed invention.

Finally, Appellants maintain that the claimed invention has unexpected properties not present in the prior art as of the August 25, 1994, priority date, as disclosed in the specification (*see, e.g.*, Amendment and Response filed January 22, 2010, pages 10-11) and set forth in the Declaration of Fatema Legrand (the "Legrand Declaration"; *see, e.g.*, Amendment and Reply to Office Action of June 17, 2011). Moreover, the showing of unexpected results was commensurate in scope and shares a nexus with the pending claims.[15]

Following the Examiner's indication during a telephone interview on April 27, 2011, that submission of data showing that self-protein analogues administered according to the claimed methods also induce autoantibodies and self-protein-specific T-cell responses against the corresponding self-proteins in humans might be sufficient to overcome the previous objection to the rebuttal evidence of unexpected results, Appellants submitted data from two clinical trials of a vaccine according to the claimed methods in the Legrand Declaration filed with the Amendment and Reply to Office Action of June 17, 2011. Predictably, the Examiner rejected the showing of unexpected results, arguing both that the additional evidence was not commensurate in scope with the pending claims and that it allegedly lacked nexus with the subject matter of the invention. Final Action, item 8, page 8.

Appellants respectfully disagree, because the evidence of unexpected results is commensurate in scope and shares a nexus with the pending claims.

The Examiner argued that the additional data presented in the Legrand Declaration "is not commensurate in scope with the claimed invention" because it discloses "experiments performed

15 The Examiner responded to the initial showing of unexpected results by arguing that it was not commensurate in scope with the claims because the claims encompassed methods of treating humans, while the experiments disclosed in the specification were performed in mice—quite remarkably, given the widespread acceptance of mice as a model organism for studying the human immune system (*see, e.g.*, Office Action of February 17, 2011, item 8, page 8).

using MVA-BN-HER2 which is a modified Vaccinia Ankara based recombinant vaccine vector derived from MVA-BN[,]" while the claimed invention "is drawn to a method of inducing autoantibodies/treatment that uses a peptide." Final Action, item 8, page 8. Citing a reference from 2011,[16] the Examiner went even further, noting that the reference "disclose[s] that the MVA-BN-HER2 vector induces immune responses that are not seen upon vaccination with protein antigen and wherein said responses are critical to the results obtained when said vaccinia vector is administered[.]" Final Action, item 8, page 9. The Examiner then concluded that "the results obtained in the Legrand Declaration clearly depend on use of the MVA-BN-HER2 recombinant vaccinia vaccine vector wherein said vector is not the claimed invention or even an invention disclosed in the specification." Final Action, item 8, page 9.

This objection must fail, because it mischaracterizes the pending claims and improperly attempts to read at least two new limitations into the claims, the first requiring use of an MVA-BN® vector encoding a HER-2 analogue, the second apparently requiring induction of specific T-cell responses and anti-tumor efficacy.

However, as discussed above, pending claim 102 recites:

> [a] method for inducing autoantibodies against a self-protein in a subject, said method comprising:
> *administering to the subject an analog of the self-protein* made by molecular biological means, wherein said analog is made by substituting one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes selected from ovalbumin, hen egg lysozyme, tetanus toxoid, or diphtheria toxoid T-cell epitopes,
> such that the secondary and tertiary structure of the self-protein is preserved to a large extent; *such that said analog induces an autoantibody response as evidenced by antibody binding to the unmodified self-protein*

(emphasis added).

16 S.J. Mandl et al., "Immunotherapy with MVA-BN®-HER2 induces HER-2-specific Th1 immunity and alters the intratumoral balance of effector and regulatory T cells," *Cancer Immunol. Immunother.* 61:19-29 (2012), published online August 7, 2011.

Thus, pending claim 102 *does not limit the 'administering' step to administration of a particular composition, formulation or route of delivery*, but simply recites "*administering to the subject an analog of the self-protein made by molecular biological means*[.]" As one of ordinary skill in the art[17] would understand, the phrase 'an analog of the self-protein made by molecular biological means' encompasses both a recombinant self-protein analogue and a recombinant viral vector comprising a gene encoding that same self-protein analogue. Administration of recombinant self-protein analogues in either form was within the level of ordinary skill in the art at the time of filing, and as the Examiner must know, the specification "need not disclose what is well-known . . . and preferably omits that which is well-known" to those skilled in the art. MPEP § 2164.05(a) (internal citations omitted).

Furthermore, despite the Examiner's insistence that certain types of immune responses induced by administration of a self-protein analog (*e.g.*, HER-2) according to the present claims encoded by a recombinant vaccinia vector (*e.g.*, MVA-BN®-HER-2 protein) but not by vaccination with a recombinant self-protein alone (*e.g.*, modified HER-2 protein), "are critical to the results obtained", the plain language of the claim recites only "such that said analog induces an autoantibody response as evidenced by antibody binding to the unmodified self-protein." Had the Examiner reviewed the Supplemental Material accompanying the Mandl reference, he would have found several pages replete with data showing that either type of self-protein analog (*i.e.*, modified recombinant HER-2 protein or MVA-BN® encoding a modified HER-2 analogue) induced HER-2-specific autoantibodies. *See, e.g.*, Supplementary Figure 1. In fact, Supplementary Figure 1A shows that treatment with HER2 formulated in Complete Freund's Adjuvant actually induced a higher titer of anti-HER-2 antibodies than treatment with MVA-BN®-HER2.

17 The term "one of ordinary skill in the art" ought to encompass Examiner Schwadron, given that he has a Ph.D. and postdoctoral experience in Immunology.

Finally, the Examiner asserted that "said vaccinia vector uses a modified tumor antigen wherein the use of tumor antigens is not disclosed in the specification. In addition, the elected species (aka TNFalpha) is not a tumor antigen." Final Action, item 8, page 9.

However, the specification teaches general strategies for modifying self-proteins such that they are capable of breaking immunological tolerance and inducing an autoantibody response. As the Examiner must know, some self-proteins, such as HER-2, are tumor antigens. Therefore, the disclosure of the specification encompasses the use of tumor antigens, and the evidence contained in the Legrand Declaration is commensurate in scope and has nexus with pending claims 102, 103, 105, and 111.

For at least this reason, the rejection of claims 102, 103, 105, and 111 as allegedly obvious over Russell-Jones in view of Dean and Bona must be reversed.

C. Rejection of Claim 111 under 35 U.S.C. § 103(a).

The Examiner rejected claim 111 under 35 U.S.C. § 103(a) as allegedly obvious over Russell-Jones, in view of Dean and Bona as applied to claim 102 above, and further in view of WO 1993/005810 ("Hellman") and US Patent No. 5,698,195 ("Le"). In particular, the Examiner asserted that the rejection of claim 102 (*see* Section VII.B. above) rendered obvious the claimed invention "except for the use of TNFα[,]" but cited Hellman for allegedly teaching that "modulation of self-proteins responsible for manifestations of a particular disease can be achieved" by eliciting antibodies to a particular self-protein by administering the self-protein conjugated to a carrier comprising a T_H-cell epitope and Le for allegedly teaching that anti-TNFα antibodies can be used to treat TNFα-mediated diseases in humans. Final Action, item 9, page 12. The Examiner therefore concluded that "[i]t would have been *prima facie*[] obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention[.]" *Id.*

Appellants respectfully disagree for at least the reasons set forth in Section VII.B. above regarding the rejection of claim 102 under 35 U.S.C. § 103(a). In addition, neither Hellman nor Le remedies the additional deficiencies of Russell-Jones discussed in detail above. Indeed, neither Hellman nor Le teaches or suggests substituting any of the T-cell epitopes recited in the pending claims as amended into a self-protein, or that a self-protein with a T-cell epitope substituted within it can induce an autoantibody response as shown by autoantibody binding to the unmodified self-protein. The sheer number of references cited in combination, and the fact that they are taken from different fields suggests that the Examiner is making an impermissible hindsight determination.

Consequently, the Examiner has not established a *prima facie* case of obviousness. Therefore, the rejection of claim 111 as allegedly obvious over Russell-Jones, in view of Dean and Bona, and further in view of Hellman and Le, must be reversed.

D. Rejection of Claims 103 and 105 under 35 U.S.C. § 103(a).

The Examiner rejected claims 103 and 105 under 35 U.S.C. § 103(a) as allegedly obvious over Russell-Jones in view of Dean and Bona as applied to claim 102 above, and further in view of US Patent Publication No. US 2003/0099634 A1 ("Vitiello"). In particular, the Examiner asserted that the rejection of claim 102 (*see* Section VII.B. above) rendered obvious the claimed invention "except for use of the ovalbumin epitope recited in claim 105[,]" but cited Vitiello for allegedly teaching an immunogenic peptide comprising the ovalbumin epitope and concluded that "[i]t would have been *prima facie*[] obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention[.]" Final Action, section 10, page 13.

Appellants respectfully disagree for at least the same reasons set forth in Section VII.B. alone regarding the rejection of claim 102 under 35 U.S.C. § 103(a). Moreover, Vitiello does not remedy the additional deficiencies of Russell-Jones discussed in detail above. For example, Vitiello does not teach or suggest substituting any T-cell epitope into a self-protein such that the secondary and

tertiary structure of the self-protein is essentially preserved. Certainly, Vitiello does not teach or suggest substituting any of the T-cell epitopes recited in the pending claims into a self-protein, or that a self-protein with a T-cell epitope substituted within it can induce an autoantibody response as shown by autoantibody binding to the unmodified self-protein.

Consequently, the Examiner has not established a *prima facie* case of obviousness. Therefore the rejection of claims 103 and 105 as allegedly obvious over Russell-Jones, in view of Dean and Bona, further in view of Vitiello must be reversed.

VIII. Conclusion

For at least the reasons given above, pending claims 102, 103, 105, and 111 are allowable and reversal of the Examiner's rejections is respectfully requested.

In the event that the United States Patent & Trademark Office ("USPTO") determines that an extension of time under 37 C.F.R. § 1.136 or other relief is required to obtain entry of this Appeal Brief, Appellants hereby respectfully request such extension or relief. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, kindly charge such fees to **Deposit Account 50-5338**, referencing Docket No. **BNIT0003-PCT-US**. However, the Commissioner is not authorized to charge the Issue Fee to the Deposit Account.

Respectfully submitted,

Dated: June 11, 2012

By: /David C. Hoffman/

David C. Hoffman, Ph.D., J.D.
Reg. No. 59,821
BN ImmunoTherapeutics, Inc.
2425 Garcia Avenue
Mountain View, CA 94043-1106
Phone: (650) 681-4780
E-mail: David.Hoffman@bn-it.com

IX. Claims Appendix to Appeal Brief Under Rule 41.37(c)(1)(viii)

As noted in Section IV. above, claims 88 and 102 include the amendments filed by Appellants on June 17, 2012.

1-87. (Canceled).

88. (Withdrawn) An autovaccine against self-proteins in humans or animals comprising:

an analog of a self-protein made by substituting one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes selected from ovalbumin, hen egg lysozyme, tetanus toxoid, or diphtheria toxoid T-cell epitopes,

such that the secondary and tertiary structure of the self-protein is preserved to a large extent; such that said analog induces an autoantibody response as evidenced by antibody binding to the unmodified self-protein; and

a pharmaceutically acceptable adjuvant.

89. (Withdrawn) The autovaccine of claim 88, wherein the pharmaceutically acceptable adjuvant is selected from the group consisting of calcium phosphate, saponin, quil A and biodegradable polymers.

90. (Withdrawn) The autovaccine of claim 88, wherein the pathogenic self- protein analog is present in the form of a fusion protein with an immunologically active cytokine.

91. (Withdrawn) The autovaccine of claim 90, wherein the immunologically active cytokine is selected from the group consisting of GM-CSF and interleukin 2.

92. (Withdrawn) The autovaccine of claim 88, wherein the pathogenic self-protein is TNFα or γ-interferon.

93. (Withdrawn) A method for the treatment of cachexia comprising administration of an effective amount of the autovaccine of claim 92.

94. (Withdrawn) The autovaccine of claim 88, wherein the pathogenic self-protein is IgE.

95. (Withdrawn) A method for the treatment of allergy comprising administration of an effective amount of the autovaccine of claim 94.

96. (Withdrawn) The autovaccine of claim 88, wherein the pathogenic self-protein is TNFα, TNFβ or interleukin 1.

97. (Withdrawn) A method for the treatment of chronic inflammatory diseases comprising administration of an effective amount of the autovaccine of claim 88.

98. (Withdrawn) A method for the treatment of rheumatoid arthritis or inflammatory bowel disease comprising administration of an effective amount of the autovaccine of claim 88.

99. (Withdrawn) The autovaccine of claim 88, wherein the pathogenic self-protein is TNFα.

100. (Withdrawn) A method for the treatment of diabetes mellitus comprising administration of an effective amount of the autovaccine of claim 99.

101. (Canceled).

102. (Previously presented) A method for inducing autoantibodies against a self-protein in a subject, said method comprising:

administering to the subject an analog of the self-protein made by molecular biological means, wherein said analog is made by substituting one or more peptide fragments in the self-protein with a corresponding number of immunodominant foreign T-cell epitopes selected from ovalbumin, hen egg lysozyme, tetanus toxoid, or diphtheria toxoid T-cell epitopes,

such that the secondary and tertiary structure of the self-protein is preserved to a large extent; such that said analog induces an autoantibody response as evidenced by antibody binding to the unmodified self-protein.

103. (Previously presented) The method of claim 102, wherein one or more of the immunodominant foreign T-cell epitopes is an ovalbumin T-cell epitope.

104. (Withdrawn) The method of claim 103, wherein the ovalbumin T-cell epitope comprises SEQ ID NO:2.

105. (Previously presented) The method of claim 103, wherein the ovalbumin T-cell epitope comprises SEQ ID NO:4.

106. (Withdrawn) The method of claim 102, wherein one or more of the immunodominant foreign T-cell epitopes is a hen egg lysozyme T-cell epitope.

107. (Withdrawn) The method of claim 106, wherein the hen egg lysozyme T-cell epitope comprises SEQ ID NO:3.

108. (Withdrawn) The method of claim 106, wherein the hen egg lysozyme T-cell epitope comprises SEQ ID NO:5.

109. (Withdrawn) The method of claim 102, wherein one or more of the immunodominant foreign T-cell epitopes is a tetanus toxoid T-cell epitope.

110. (Withdrawn) The method of claim 102, wherein one or more of the immunodominant foreign T-cell epitopes is a diphtheria toxoid T-cell epitope.

111. (Previously presented) The method of claim 102, wherein the self-protein is TNFα.

112. (Withdrawn) The method of claim 102, wherein the self-protein is ubiquitin.

X. Evidence Appendix to Appeal Brief Under Rule 41.37(c)(1)(ix)

1. S.J. Mandl et al., "Immunotherapy with MVA-BN®-HER2 induces HER-2-specific Th1 immunity and alters the intratumoral balance of effector and regulatory T cells," *Cancer Immunol. Immunother.* 61:19-29 (2012), published online August 7, 2011.

2. S.J. Mandl et al., "Immunotherapy with MVA-BN®-HER2 induces HER-2-specific Th1 immunity and alters the intratumoral balance of effector and regulatory T cells," *Cancer Immunol. Immunother.* Electronic Supplementary Material, published online August 7, 2011.

Examiner Schwadron cited the Mandl reference (item 1) on a Form PTO-892 accompanying the Final Action of February 15, 2012, but provided an incomplete copy of the underlying document lacking the electronic supplementary material referenced on the front page of the article. Appellants provide a copy of the electronic supplementary material (item 2) herewith to ensure the record contains a complete copy of the reference, and because figures included as part of the supplementary material are referenced in this Appeal Brief.

XI. Related Proceedings Appendix to Appeal Brief Under Rule 41.37(c)(1)(x)

No decisions in related proceedings are being cited in this Appeal Brief.